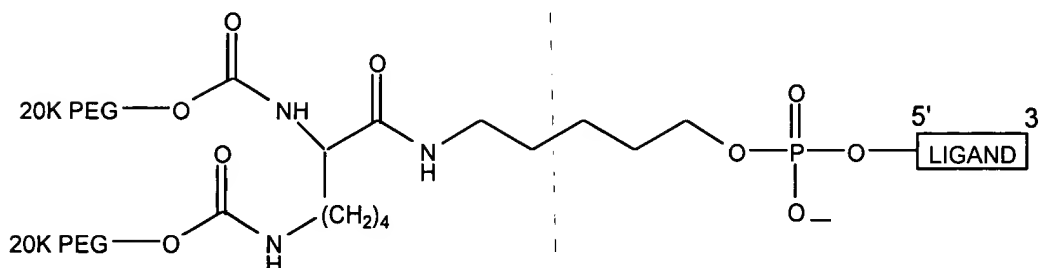


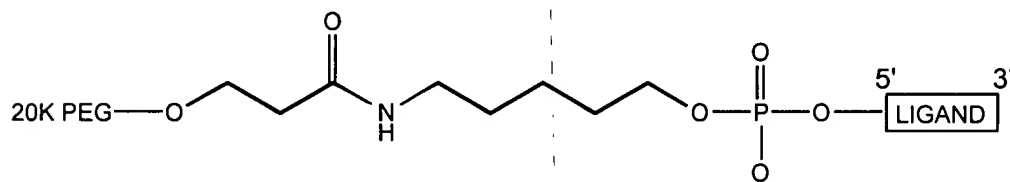
20. The method of claim 19 wherein said complex has the structure



Ligand Component =

fCmGmGrArAfUfCmAmGfUmGmAmAfUmGfCfUfUmAfUmAfCmAfUfCfCmG-3'3'-dT  
(VEGF ligand)

21. The complex of claim 19 wherein said complex is



Ligand Component =

fCmGmGrArAfUfCmAmGfUmGmAmAfUmGfCfUfUmAfUmAfCmAfUfCfCmG-3'3'-dT  
(VEGF ligand)

### REMARKS

An Office Action was issued in the above-referenced application on June 8, 1998. All examined claims were rejected. This Amendment and Remarks has been made to respond to such Office Action. Claim 2 is amended and claims 3-21 are added herein. Additional amendments have been made by the Applicants without suggestion by the Examiner, but with the same goal in mind. Any amendments that are made that limit the scope of the claims in any way are done so without prejudice. Claims 3-21 are dependent on either claim 1 or claim 2 and relate to embodiments that are clearly supported in the specification.

#### Notice to Comply with Sequence Rules

Applicants submitted a response to the Notice to Comply with Requirements for Patent Applications containing Nucleotide Sequence and/or Amino Acid Sequence Disclosures on July 7, 1998.

#### Informalities

The Examiner has objected to the disclosure because nucleotide sequences in the specification, tables and figures lack SEQ ID NOS. Applicants have added the appropriate SEQ ID NOS to Tables 1-4 and Figures 1A-1E and are submitting substitute tables and figures with this document. Furthermore, the specification has been amended to include SEQ ID NOS where appropriate. Applicants assert that the amendments and the substitute tables and figures do not add any new matter to the application or affect the claimed invention. Withdrawal of this objection is respectfully requested.

#### Rejections under 35 U.S.C. §112, second paragraph

Claim 2 is rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The claim has been amended to specifically address points (a), (b), and (d).

With respect to point (c), the Examiner states that the claim is indefinite in reciting "nucleic acid ligand" which is a general term lacking definition or specificity. Applicants respectfully disagree. Applicants wish to direct the Examiner's attention to page 17, lines 4-26 of the specification where Nucleic Acid Ligand is specifically defined. There is no apparent ambiguity with respect to the definition of this term. As this term has been clearly defined in the specification, withdrawal of this rejection is respectfully requested.

#### Double Patenting Rejection - Obviousness Type

Claim 1 is provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 5-8 and 11-13 of United States Patent Application No. 08/447,169 (now United States Patent No. 5,811,533) in view of Toole et al. (WO 92/14843). In an effort to expedite prosecution,

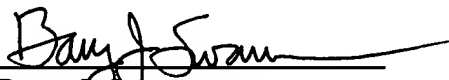
Applicants are submitting herewith a Terminal Disclaimer that disclaims the term of the patent issuing on the subject application beyond the term of the aforementioned patent. NeXstar Pharmaceuticals, Inc., is the assignee of record of the entire interest in United States Patent No. 5,811,533. Thus, NeXstar Pharmaceuticals, Inc. is the owner of the subject application and the patent cited by the Examiner. In view of this submission, it is respectfully requested that the provisional obviousness-type double patenting rejection be withdrawn.

Applicants assert that the above-captioned application is in condition for allowance. Prompt consideration of this Amendment and Remarks is earnestly solicited.

This constitutes a request for any needed extension of time and an authorization to charge all fees therefore to Deposit Account No. 22-0277, if not otherwise specifically requested. In addition, the undersigned hereby authorizes the charge of any fee created by the filing of this document to Deposit Account No. 22-0277.

Respectfully submitted,

Date: December 7, 1998

  
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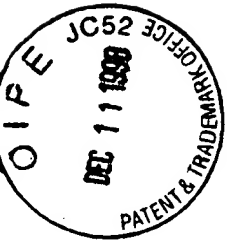


Table 1. 2'-F-pyrimidine ligands to VEGF165

Ligand (frequency)	Sequence of variable region 5'-gggaggacgauggg [variable region] cagacgacugcccgga-3'	K <sub>d</sub> (pM)	SEQ. ID NO: 10 & 11
Family 1			
VP30.7	g AAGAAUUGG UCAUCGUCGUCUCCGCCUCCC	3000	12
VP30.12	AAUACG GAAGAAUUGG AUACAUAUGCUCGU	7	13
VP30.13 (7)	GAUAACA GAAGAAUUGG UGAACAACGUGGU	10	14
VP30.16	AUGAUCGCGUAG GAAGUAUUGG AAGGCCCU	6	15
VP30.19	CACUUUA GAAGAAUUGA AUUCCCGCUGGU	9	16
VP30.22 (6)	UAG GAAGAAUUGG AAGCGCAUUUCCGCGY	20	17
VP30.25	CGGGAUUUUG GAAGAAUUGG AUAUUGGCCU	20	18
VP30.26 (2)	CGGYACUUUG GAAGAAUUGA AUUCCCGCGU	10	19
VP30.27	g AAGAAUUGG AUAUAUCGUUACCCCCACCU	400	20
VP30.40	AAACG GAAAGAAUUGG AUACGCAAGCAGUU	6	21
VP30.41	UAG GAAGUAUUGU AAGCGCUCGUUUUUCGC	7	22
VP30.51 (2)	AGUUUUG GAAGAAUUGG AUGUCCCGAUCGU	90	23
VP30.54	AAGAAACG GAAGAAUUGG AGACAGCUCGU	10	24
VP40.4 (5)	g GAAGAAUUGA UGUUGUAUUGUCCGUAUUCCUGCCGU	200	25
VP40.43	ACA GAAGAAUUGG GCUUCGCAUUAUCCUCUGUCAGCCGC	30	26
VP40.53	UGAGAGAAACG GAAGAAUUGG AUACGAUACUCAUCGCGCU	8	27
VT30.4	CUUAAGUUUUG GAAGAAUUGA AUACUGGGU	20	28
VT30.7	UAACCAUG GAAGAAUUGG CUGCUAUCCU	10	29
VT30.10	AACG GAAGAAUUGG AUACGUAGCAUGCGU	2	30
VT30.13	CAGGAUUUUG GAAGAAUUGG AUAUUGGCCGca	10	31
VT30.20	AAACG GAAGAAUUGG AUACCGCUACGUGUU	4	32
VT30.52	g AAGAAUUGA GCAUCCUUCUCCUUGUGCCU	9000	33
VT30.53	AGCUAACG GAAGAAUUGG AAACAACCGCGUc	10	34

APPROVED  
SZ 3-29-99

Ligand (frequency)      Sequence of variable region      K<sub>d</sub>      SEQ. ID. NO.:  
 5'-gggaggacgaugcgg [variable region] cagacgacucgcccga-3'      (pM)      10 & 11

Family 2

VP30.2 (5)	ggYGA	ACCGA	UGGAA	UUU	UUGGACGC	UCGCCU	10	35
VP30.5 (4)	gAYCA	ACCGA	UUGAC	GUUA	UGGACGC	UGGUc	8	36
VP30.31 (5)	gcggUA	ACCGA	UUGAA	CUUC	UUGGACGC	UACCGU	6	37
VP30.43	ggUA	ACCGAA	UUGAA	GUUA	UUGGACGC	UACCU	5	38
VP40.9	gGAGCAGA	ACCGA	UAGAA	GAA	UUGGACGC	UCAGCUCGGGU	30	39
VP40.14	GUACCAGAAUGAGCA	ACCGA	AUGAA	GAA	CUGGACGC	UGCUca	8	40
VP40.17	ugcggUGA	ACCGA	UGGAA	UCGC	UUGGACGC	UCAUGGCACGUUGCU	10	41
VT30.9 (6)	ggUCA	ACCGG	UUGAA	UAU	UUGGUCGC	UGACCU	30	42

Family 3

VT30.1 (2)	gacgaugcgg	A	ACUA	GUGAAUGCUU	AUA	CGA	CCGUGUUGUc	10	43
VT30.2	gcgg		AUCA	GUGAAUGCUU	AUA	GA	CCGCCUCCGU	2	44
VT30.3 (8)	gaugcgg	AGA	AUCA	GUGAAUGCUU	AUA	AAUC	UCGYGUc	5	45
VT30.11	gaugcgg	A	AUCA	GUGAAUGCUU	AUA	GCUC	CCGCCGUCCU	4	46
VT30.15	gcgg	A	ACCA	GUGAAUGCUU	AUA	AGA	CUGCUCGU	3	47
VT30.21	cgaugcgg		AUCA	GUGAAUGCUU	AUA	GA	CCGUAUUUGCGU	6	48
VT30.28	gaugcgg	AGA	AUCA	GUGAAUGCUU	AUA	AACC	UCGUGUc	60	49
VT30.29	augcggA		AUCA	GUGAAUGCUU	AUA	GC	UCCCGGUGGU	10	50
VT30.35	cgg		ACCA	GUGAAUGCUU	AUA	AGCCCA	UCGACCU	N.D.	51
VT30.41	gaugcgg		CAGG	GUGAAUGCCA	AUG	UACUUU	UCGGGUc	40	52
VT30.44	gcggA		AUCA	GUGAAUGCUU	AUA	CA	UCCGCUCGGU	10	53
VT30.54	gcggG		ACUAG	GUGAAUGCCA	AUA	UUCUUC	UCCGU	10	54

Table 2. Effect of truncation on high affinity binding of VEGF ligands.

Ligand	Sequence	Length (nts)	K <sub>D</sub> (pM)	SEQ ID NO:
t22	GACGAUGCGGUAGGAAGAAUUGGAAGCGC*	29	70	55
t22a	GACGAUGCGGUAGGAAGAAUUGGAAGCG	28	3000	56
t22b	ACGAUGCGGUAGGAAGAAUUGGAAGCGC	28	80	57
t22c	GCGGUAGGAAGAAUUGGAAGCGC	23	90	58
t22d	CGGUAGGAAGAAUUGGAAGCGC	22	100	59
t22e	GGUAGGAAGAAUUGGAAGCGC*	21	200	60
t22f	GUAGGAAGAAUUGGAAGCGC*	20	>100,000	61
t2	GGCGAACCGAUGGAAUUUUUGGACGCUCGCC*	31	20	62
t2a	GCGAACCGAUGGAAUUUUUGGACGCUCGC	29	40	63
t2b	CGAACCGAUGGAAUUUUUGGACGCUCG	27	100	64
t2c	GAACCGAUGGAAUUUUUGGACGCUC*	25	200	65
t2d	AACCGAUGGAAUUUUUGGACGCU*	23	20,000	66
t2e	ACCGAUGGAAUUUUUGGACGC*	21	>100,000	67
t44	GCGGAAUCAGUGAAUGCUUAUACAUCCGC*	29	10	68
t44a	CGGAAUCAGUGAAUGCUUAUACAUCCG	27	10	69
t44b	GGAAUCAGUGAAUGCUUAUACAUC	25	60	70
t44c	GAAUCAGUGAAUGCUUAUACAUC*	23	2000	71
t44d	AAUCAGUGAAUGCUUAUACAUC*	21	>100,000	72
t44e	AUCAGUGAAUGCUUAUACA*	19	>100,000	73

**Table 3. Effect of 2'-OMe-purine substitutions on affinity for VEGF.**

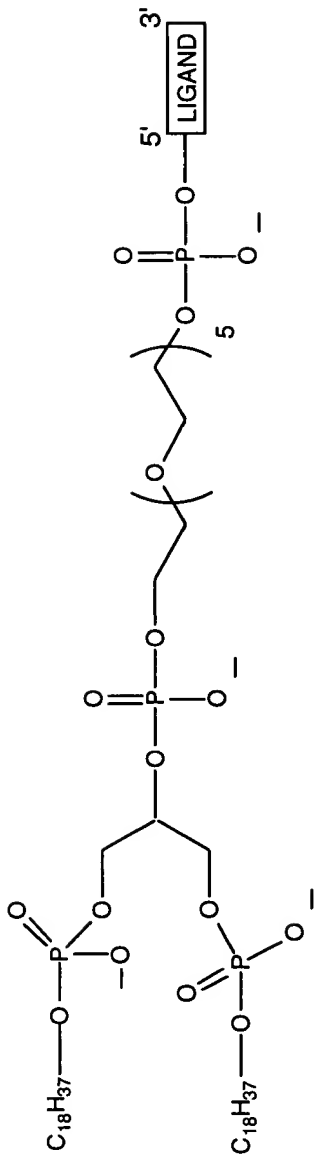
T670P

Ligand	Sequence	K <sub>D</sub> (pM)	SEQ NO:
t22OMe (OH-10,12,22)	<b>GACGAUGCGGU<u>A</u>GGAAGAAUUGGAAGCGC</b>	10	74
t22OMe (OH-10,12)	<b>GACGAUGCGGU<u>A</u>GGAAGAAUUGGAAGCGC</b>	20	75
t22OMe (OH-10,22)	<b>GACGAUGCGGU<u>A</u>GGAAGAAUUGGAAGCGC</b>	4,000	76
t22OMe (OH-12,22)	<b>GACGAUGCGGU<u>A</u>GGAAGAAUUGGAAGCGC</b>	90	77
t2OMe (OH-6,21)	<b>GGCGA<u>A</u>CCGAUGGAAUUUUUGGACGCUCGCC</b>	60	78
t2OMe (OH-6)	<b>GGCGA<u>A</u>CCGAUGGAAUUUUUGGACGCUCGCC</b>	500	79
t2OMe (OH-21)	<b>GGCGA<u>A</u>CCGAUGGAAUUUUUGGACGCUCGCC</b>	20,000	80
t44OMe (OH-5,6)	<b>GCGGA<u>A</u>UCAGUGAAUGCUUAUACAUCCGC</b>	40	81
t44OMe (OH-5)	<b>GCGGA<u>A</u>UCAGUGAAUGCUUAUACAUCCGC</b>	>100,000	82
t44OMe (OH-6)	<b>GCGGA<u>A</u>UCAGUGAAUGCUUAUACAUCCGC</b>	>100,000	83

Table 4. Binding Parameters of 2'-Ome-substituted minimal ligands.

Ligand	Sequence	K <sub>D</sub> (s.d.) (pM)	k <sub>d</sub> (s.d.) (sec <sup>-1</sup> )	k <sub>a</sub> (M <sup>-1</sup> sec <sup>-1</sup> )	SEQ ID NO:
t22OMe	GCGGUAGGAAGAAUUGGAAGCGC	67 (36)	0.012 (0.004)	1.8 x 10 <sup>8</sup>	84
t2OMe	GCGAACCGAUGGAUUUUUGGACGUCGC	140 (50)	0.0042 (0.002)	3.0 x 10 <sup>7</sup>	85
t44OMe	CGGAAUCAGUGAAGCUGUAUACAUCCG	51 (11)	0.0074 (0.002)	1.5 x 10 <sup>8</sup>	86



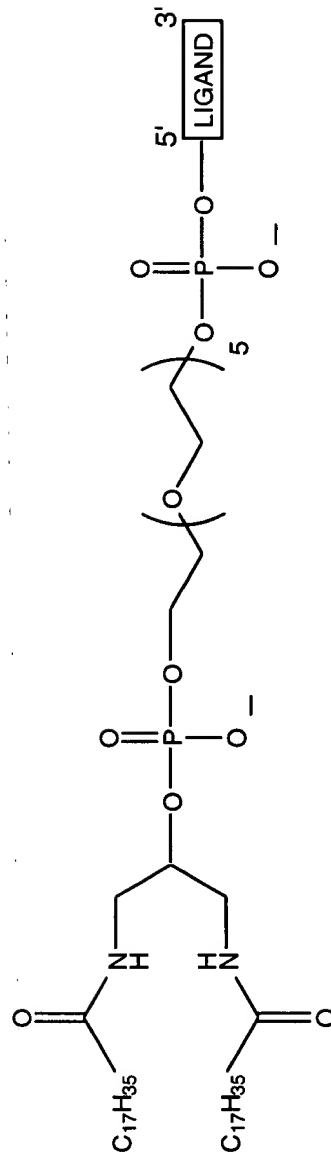


NX31838 - PL

Ligand Component =

fCmGmGrArAfUfCmAmGfUmGmAmAfUmGfCfUfUmAfUfCmAfUfCfCmG-3'3'-dT  
(VEGF ligand)

FIGURE 1A SEQ. ID NO.: 5



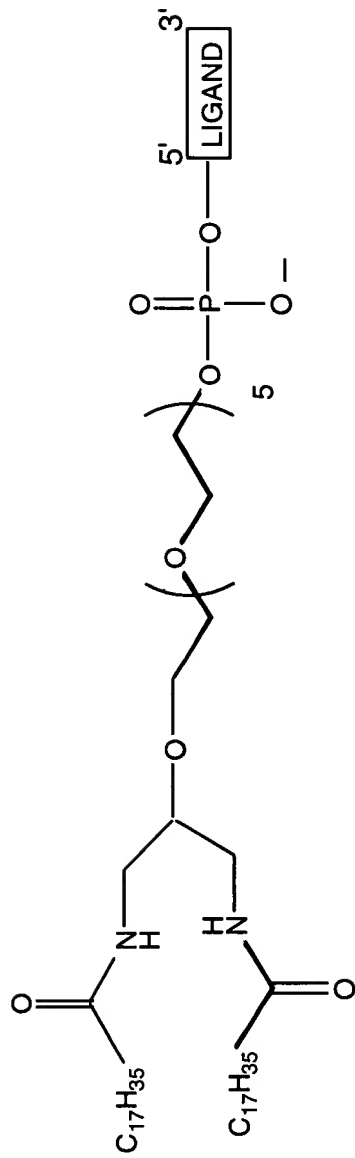
NX31838 Lipid-amide 1

Ligand Component =

fCmGmGrArAfUfCmAmGfUmGmAmAfUmGfCfUfUmAfUfCmAfUfCfCmG-3'3'-dT  
(VEGF ligand)

FIGURE 1B SEQ. ID NO.: 6

Approved  
3-25-epi

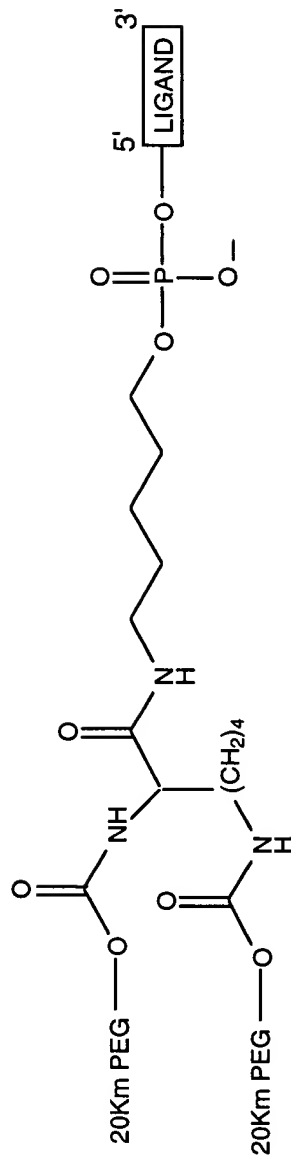


NX31838 Lipid-amide 2

Ligand Component =

fCmGmGrArAfUfCmAmGfUmGmAmAfUmGfCfUfUmAfUmAfCmAfUfCfCmG-3'3'-dT  
(VEGF ligand)

FIGURE 1C SEQ. ID NO.: 7

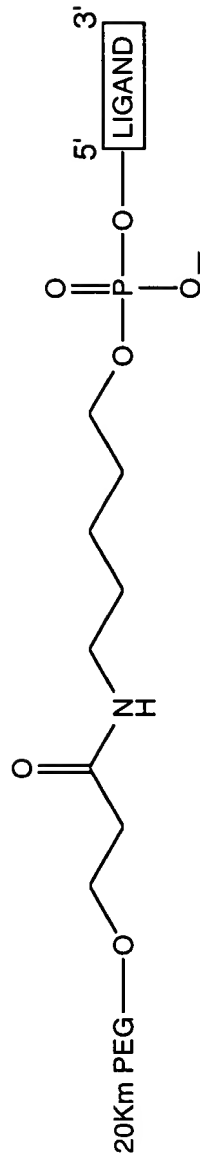


NX31838 40K mPEG

Ligand Component =

fCmGmGrArAfUfCmAmGfUmGmAmAfUmGfCfUfUmAfUmAfCmAfUfCfCmG-3'3'-dT  
(VEGF ligand)

FIGURE 1D SEQ. ID NO.: 8



NX31838 20Kb PEG

Ligand Component =

fCmGmGrArAfUfCmAmGfUmGmAmAfUmGfCfUfUmAfUmAfCmAfUfCfCmG-3'3'-dT  
(VEGF ligand)

FIGURE 1E SEQ. ID NO.: 9